

ROLE OF INTRAVITREAL BEVACIZUMAB IN THE TREATMENT OF NEOVASCULAR GLAUCOMA

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CONTENTS

Introduction	1
Aim of the study	3
Review of literature	4
Materials and Methods	37
Results	41
Discussion	45
Conclusion	50

Bibliography

Proforma

Master charts

Introduction

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide ¹ accounting for about 67 million sufferers.

In glaucoma there is characteristic optic neuropathy with irreversible damage to the retinal ganglion cells leading to optic nerve head damage associated with corresponding visual field loss for which elevated IOP is one of the important risk factors.

Neovascular glaucoma (NVG) is a type of potentially devastating secondary glaucoma caused by fibrovascular membrane formation over the iris, angle of anterior chamber and trabecular meshwork leading to progressive angle closure.

It is due to an ongoing pathology causing retinal ischemia, leading to production of vaso proliferative substances which diffuse into anterior segment, in turn causing new vessel growth over the iris and angle. The IOP is often difficult to control resulting in loss of vision.

There are various modalities of treating this NVG. Retinal ischemia being the main cause should be treated for which the main stay of treatment is Pan Retinal Photocoagulation (PRP), which ablates the ischemic retina and reduces

the VEGF production. IOP can be reduced medically by aqueous production reducing drugs; surgically by trabeculectomy and shunt surgeries.

Raised IOP is more refractory to medical management alone. Due to new vessel growth, surgical mode of treatment has high incidence of complications and failure rate. Another effective and novel method is by counteracting the angiogenesis factor, VEGF, thereby reducing the new vessel formation over the iris and angle, by anti VEGF agents like Bevacizumab. The intravitreal use of the same has been studied with good results.

Aims of the study

AIMS OF THE STUDY

To evaluate the role of intravitreal Bevacizumab in Neovascular glaucoma:

- a. Evaluating regression of neovascularization of the iris
- b. IOP control
- c. Side effects
- d. Need of additional intervention following intravitreal Bevacizumab

Review of literature

REVIEW OF LITERATURE

NEOVASCULAR GLAUCOMA

Neovascular glaucoma (NVG) is a type of potentially devastating secondary glaucoma caused by fibrovascular membrane formation over the iris, angle of anterior chamber and trabecular meshwork leading to progressive angle closure.

The underlying pathology is retinal ischemia, leading to production of vaso proliferative substances which diffuse into anterior segment, in turn causing new vessel growth over the iris and angle. The IOP is often difficult to control resulting in loss of vision.

HISTORY

As early as 1871, Pagenstecher documented eye with intraocular bleeding and elevated IOP as having hemorrhagic glaucoma².

The anatomical basis for NVG being the histological finding of new vessel on the iris was first put forward by Coats in 1906 in an eye with CRVO³.

In 1928, Salus described similar new vessels on iris of eyes of diabetic patients. With the introduction of clinical gonioscopy in 1963, Kurtz described his clinical observation of new vessels in the angle.

In 1963, Weiss and colleagues proposed the term neovascular glaucoma as the glaucoma is caused by new vessels. Waston and Grant in 1968, proposed the term Neovascularization of Iris (NVI) rather than rubeosis iridis. Historically NVG was termed as hemorrhagic glaucoma, thrombotic glaucoma, congestive glaucoma, rubeotic glaucoma.

CAUSES OF NEOVASCULAR GLAUCOMA

The common causes of NVG are Diabetic retinopathy (43 %), and CRVO (37 %), Carotid artery occlusive disease (CAOD). Inflammatory without retinal ischemia accounts for only 3 %.

OCULAR VASCULAR DISEASES

A. Retinal vascular occlusive diseases

1. Central retinal vein occlusion.
2. Hemi retinal vein occlusion.
3. Branch retinal vein occlusion

B. Diabetic retinopathy.

- C. Eales disease
- D. Sickle cell retinopathy.
- E. Coats disease
- F. PHPV
- G. Ocular tumors
 - 1. Retinoblastoma
 - 2. Uveal melanoma
 - 3. Metastatic tumor

OTHER OCULAR DISEASES

- A. Inflammatory diseases
 - 1. Chronic uveitis
 - 2. Vogt – koyanagi – harada syndrome
 - 3. Endophthalmitis
 - 4. Syphilitic retinitis
 - 5. Sympathetic ophthalmitis
- B. Long standing rhegmatogenous rd
- C. Sticklers syndrome

EXTRA OCULAR VASCULAR DISEASES

- 1. Carotid occlusive disease
- 2. Pulseless disease

3. Giant cell arteritis
4. Neurofibromatosis
5. Caroticocavernous fistula

RADIATION

- a. External beam
- b. Charged particle – proton, helium
- c. Photoradiation.

Central retinal vein occlusion

CRVO is one of the most common causes of NVG. It accounts for one third of the cases. May be ischemic or nonischemic Nonischemic do not progress to NVG. 40 % of ischemic CRVO go for NVG. One third to half of the nonischemic type turns into Ischemic CRVO. Greater the degree of capillary nonperfusion, greater the chances of neovascularization. This is confirmed by fluorescein angiography. So careful follow up and repeated angiography is needed for a prophylactic treatment.

Diabetes mellitus

Diabetic retinopathy (DR) is the second most common cause of NVG. In DM with PDR, the incidence of NVI is up to 65 %. The basic pathology being hyperglycemia, leading to retinal hypoxia. Onset of DR is related to the duration of the disease and is more with Type – II DM. Capillary dropout and retinal

hypoxia occurs after surgical procedures like cataract extraction and vitrectomy in patients with DM. This adds to the risk of developing neovascularization. Increased incidence of NVI is also seen in absence or removal of diffusion barrier posterior capsule – anterior hyaloid.

Carotid artery occlusive disease

CAOD is the third most common cause of NVG, accounting for 13 %. Decreased perfusion of ciliary body from CAOD may decrease aqueous production with normal or low IOP.

Central artery occlusion

The incidence of isolated CRAO is 7 %. In CRAO, there is destruction of the inner retinal layer and capillary endothelium which explains no retinal neovascularization. NVD in CRAO is due to new vessels from choroidal circulation. There is no viable retinal tissue. It has been proposed that there is first CAOD, which causes anterior segment ischemia leading to NVI and NVG. Decreased perfusion of CRA makes it susceptible to occlusion. Increased IOP is from the already existent NVG.

Retinoblastoma

Retinoblastoma cells contain VEGF, mRNA and hypoxic conditions together resulting in increased production of VEGF which in turn causes NVI and NVG.

Malignant melanoma

Occurrence of NVI correlates with increased tumor size, tumor necrosis and extent of overlying retinal detachment. NVI and NVG is also caused by irradiation which is used in treatment of malignant melanoma. VEGF and VEGF mRNA are not detected in the cells and hypoxia in melanoma cell line does not increase VEGF production. NVI in metastatic tumors is due to direct effect of tumor secreted angiogenesis factor. NVI in Fuch's heterochromic iridocyclitis and pseudoexfoliation syndrome is due to anterior segment perfusion compromise.

PATHOGENESIS OF NVG

The basic pathology in neovascularization of iris and angle occurs in response to stimulus factor of retinal ischemia. For this process to occur viable retinal tissue, a low oxygen tension, venous drainage must be present⁴. In 1956, Wise proposed that retinal capillary or venous obstruction resulted in hypoxia of retinal cells and would produce vasoformative factor⁵. Vascular endothelial growth factor (VEGF), an endothelial cell specific mitogen is responsible for this cascade⁶

OTHER DIFFUSIBLE SUBSTANCES INVOLVED IN ANGIOGENESIS

- Pro angiogenic factor
- Tumor necrosis factor – TNF- α
- Insulin-like growth factors I and II ⁷
- Insulin-like growth factor binding proteins 2 and 3 ⁸
- Basic Fibroblast growth factor - bFGF⁹
- Platelet-derived growth factor ⁸
- Interleukin - 6 ⁸.

Under conditions of retinal ischemia VEGF is mainly synthesized by muller retinal cell. Intraocular diffusion of VEGF to anterior chamber occurs. Aphakia, posterior capsule rupture, post YAG capsulotomy have shown high incidence of rubeosis.

Endothelial cells from venules or capillaries release enzymes that disrupt the adjacent basement membrane. Adjacent endothelial cells from existing vessels migrate towards the source of the angiogenic stimulus, whereas more distal cells undergo proliferation. The endothelial cells then elongate, and lumen formation occurs. Finally, new basement membrane forms and pericytes surround the new capillaries to form mature new vessels.

The neovascularization process begins as endothelial budding from capillaries of mainly the minor arterial circle at pupil. Endothelial buds progress to become glomerulus-like vascular tufts. Being new vessels they leak fluorescein.

These new vessels are thin walled endothelial cells without a muscular layer or much adventitia or supportive tissue. There are gaps and fenestrations in between these endothelial cells ¹⁰.

These new vessel appear on the surface of the iris and oramation of fibrovascular membrane which consists of myofibroblasts. These are fibroblasts with smooth muscle differentiation ¹¹. They are clinically transparent. They are identified by flattening of the usual iris surface architecture. New vessels are actually beneath this layer of myofibroblasts. This membrane is present wherever there is new vessel. Presence of this membrane at the angle blocks the aqueous out flow increasing the IOP despite the appearance of normal open angle.

The smooth muscle component of myofibril contracts on the surface of iris, post pigment layer of the iris is pulled around the papillary margin onto the anterior surface, causing ectropion uveae. Contraction at the root of iris leads to PAS and further contraction results in synechial angle closure with iridocorneal touch. In the late stages the endothelium and descemet's membrane extends from the cornea across the synechiae onto the iris surface ¹².

CLINICAL FEATURES

- The classic feature of NVG is a patient with painful eye
- Reduced vision
- Conjunctival congestion

- Corneal edema
- Iritis / Vitritis
- Elevated IOP
- RAPD
- Neovascularization of iris
- Neovascularization of angle
- Synechial angle closure
- Optic nerve damage
- Associated Retinopathy

STAGES OF NVG¹³

The clinical and histologic events lead from a predisposing factor through rubeosis iridis to NVG may be classified as

1. Pre-rubeosis stage
2. Pre-glaucoma stage : rubeosis iridis
3. Open angle glaucoma stage
4. Angle closure glaucoma stage

PRE-RUBEOSIS STAGE

The main predisposing factors for rubeosis are diabetic retinopathy and central retinal vein occlusion. They go for rubeosis at 43 % and 37 % respectively¹⁴.

DIABETIC RETINOPATHY

High incidence of rubeosis is reported with proliferative type of DR. The risk of NVI and NVG in DR is increased when arteriolar or capillary nonperfusion or after vitrectomy or lensectomy. There is high correlation between rubeosis iridis with disc neovascularization and rhegmatogenous retinal detachment ¹³.

Before clinically detectable NVI, iris fluorescein angiography demonstrates peripupillary leakage of dye. Thus slitlamp biomicroscope is less reliable than angiography. Angle neovascularization may precede that of the iris. So treatment is needed prior to clinical detection of rubeosis.

CENTRAL RETINAL VEIN OCCLUSION

The incidence of NVI and NVG in CRVO is significantly correlated with the retinal capillary nonperfusion ¹³.

Fluorescein angiography is the most direct method of evaluating capillary non perfusion. This may not be feasible due to obstruction of visualization by blood or other media opacities.

Aqueous protein and cell concentrations by laser flare - cell meter have shown to correlate with FFA findings and severity of retinal vein occlusion. RAPD indicates the increased risk of rubeosis iridis after CRVO. ERG, flicker ERG,

color Doppler imaging of blood flow velocities of CRV and CRA provide high degree of predictability regarding NVI.

RUBEOTIC STAGE (PREGLAUCOMA STAGE)

Early in the disease process slitlamp biomicroscopy reveals dilated tufts of preexisting capillaries and fine, randomly oriented vessels on the surface of the iris near the pupillary margin. These new vessels are characterized by leakage of fluorescein. Gonioscopy reveal variable amount of angle neovascularization. These neovascular trunks cross the ciliary body band and scleral spur and arborize on the trabecular meshwork.

OPEN ANGLE GLAUCOMA STAGE

New vessel in a CRVO arises about 8 to 15 weeks after the vascular occlusive event. It has been called 90 day glaucoma because of the time interval - 3 months. Rubeosis iridis is more florid

Aqueous reveals inflammatory reaction. Gonioscopy, reveals neovascularization. Angle is open and a fibro vascular membrane covers the angle and anterior surface of iris, obstructing the aqueous out flow. The angle new vessel arborizes on and into the trabecular meshwork. The IOP is elevated with an open angle. Open angle stage is associated with anterior chamber inflammation and hemorrhage.

ANGLE CLOSURE GLAUCOMA STAGE

Stroma of the iris has become flattened, with a smooth glistening appearance. The fibrovascular contractile smooth myofibril containing tissue is responsible for tissue contraction. Ectropion uveae develops with distortion of pupil. Fibrovascular tissue contraction at the angle leads to PAS and eventually angle closure. Iris becomes flattened with a smooth glistening appearance. Iris is often dilated and pulled anteriorly. Glaucoma is severe.

MANAGEMENT

DIAGNOSIS

A careful clinical examination and history of long term underlying pathology like DR, RD is taken. Careful slit-lamp examination reveals circumcorneal congestion with corneal edema and anterior chamber inflammation. NVI with ectropion uveae may be present. IOP is usually intractably high. Fluorescein angiography shows leaking iris vessels.

TREATMENT

This may be considered under these headings.

1. Prophylactic treatment
2. Early stage therapy
3. Late stage therapy
4. End stage therapy

PROPHYLACTIC TREATMENT

Causes of NVG are multifactorial. Control of HT, blood glucose, and cholesterol levels is the best prophylaxis. Careful follow up of nonischemic CRVO and FFA in ischemic type to assess the amount of nonperfusion area is a must. In DR patients with PDR, FFA is done to find the nonperfusion areas. Prophylactic PRP to ablate ischemic retina will prevent NVI and NVG.

Retinal hypoxia leads to the expression of VEGF, being the basic pathology in developing NVI and subsequently NVG. Anti VEGF treatment will be good prophylaxis in vitreous with hemorrhage in PDR, Eale's disease.

PEDF (pigment epithelial derived factor) a potent angiogenesis may be administered therapeutically or by viral mediated gene transfer¹⁵.

EARLY STAGE THERAPY

Once NVI is discovered, the mainstay in early therapy is PRP. There is 60% decrease in vitreous VEGF levels after the laser treatment¹⁶.

During standard PRP, only 13 % of the retinal area is treated. According to guidelines of the Diabetic Retinopathy Study, a minimum of 1200 - 1600, 500µm sized burns applied randomly over the peripheral retina. This study also states, eyes that had more PRP had less risk of visual loss¹⁷. So most specialists

believe that 1500 – 2000 spots using Rodenstack wide angle contact lens (670µm spot size) is necessary to constitute adequate PRP. Krypton laser is more effective if some media opacity or retinal hemorrhages is present.

If adequate PRP is given early in the course of NVI, there is regression of NVI in CRVO and PDR. If the cause is a detached retina or an ocular tumor the early therapy must be directed to the primary cause.

ENDOPHOTOCOAGULATION

It is done in situations where preoperative PRP is not possible in eyes with NVI. This procedure is widely done in vitreous hemorrhage during vitrectomy.

PANRETINAL CRYOTHERAPY

It is indicated in cases in which cornea, lens, or vitreous is too hazy for adequate PRP. Produces more inflammation and blood-retinal barrier breakdown. After the procedure there is increased influx of macrophages, which has an added benefit of clearing vitreous blood.

GONIOPHOTOCOAGULATION

Direct laser treatment of NVI eliminates angle vessel in the treated area. It also prevents further angle closure. Goniophotocoagulation alone is not beneficial. The success rate depends upon adjuvant PRP.

MEDICAL THERAPY

All the anti glaucoma medications will be effective to some degree in lowering IOP. Two medicines of greatest benefit is, topical Atropine 1 % twice a day which reduces ocular congestion. Topical steroids is used four times daily to reduce ocular inflammation.

LATE – STAGE THERAPY

PAN RETINAL PHOTOCOAGULATION

When synechial angle closure has occurred, it is considered the late stage. If possible PRP should still be performed to eliminate the stimulus for new vessel formation. PRP does not prevent or reverse the synechial formation but it causes regression of new vessels. Regression of new vessel occurs within days. Without elimination of new vessel formation, filtration surgery more likely to fail. Preferably 3– 4 weeks, should elapse between completed PRP and filtration surgery.

MEDICAL THERAPY

With extensive synechial closure is established, medications acting on aqueous out flow are useless (Pilocarpine). Moreover they are contraindicated as they increase hyperemia and inflammation. Medications that decrease aqueous production, such as β -blockers and carbonic anhydrase inhibitors, are beneficial.

Topical Apraclonidine is effective on short term basis. Brimonidine and prostaglandin analogues have not been evaluated in late stage NVG. Osmotic agents can be used intermittently to clear the cornea.

The most important medications are topical atropine and steroids to decrease congestion and inflammation¹⁸.

CONVENTIONAL SURGERY

If there are engorged iris vessels at the time of surgery, intraoperative and postoperative hemorrhages are likely to occur. The presence of active neovascularization leads to late bleb failure by conjunctival scarring at the filtration site.

To prevent postoperative scarring of the filtration bleb, β -irradiation.¹⁹, Subconjunctival injection of 5-fluorouracil²⁰ and intraoperative Mitomycin – C²¹ have been tried. Whatever the surgical procedure, PRP should be performed whenever possible²².

FILTRATION TECHNIQUE

After adequate PRP, topical atropine and steroids are instilled. If IOP is high, aqueous production reducing drugs and osmotic agents are used preoperatively. This avoids sudden surgical decompression of the hard eye.

Peribulbar or retrobulbar anesthesia with epinephrine plus orbital massage is preferred.

A full thickness procedure (e.g.: a trephine or posterior lip sclerectomy) or a guarded procedure (e.g.: a trabeculectomy) may be performed. Preference is to perform trabeculectomy with MMC.

Preiridectomy-cautery to the iris is done when iris is lifted by forceps to prevent bleeding. Postoperative medication includes topical steroids six times per day, Cycloplegic agent twice; NSIAD topical drops four times, topical antibiotics six times daily. Surgical success of IOP less than 25 mmHg was reported to be 70 % to 80 %.

GLAUCOMA TUBE IMPLANT SURGERY

Filtration surgery in NVG should be reserved for eyes that have useful vision. Major problem with filtration surgery in NVG is failure of filtration bleb through episcleral scarring. This lead to the thought of maintaining an opening between anterior chamber and subconjunctival space has formed the basis for various Seton procedures. Implants are widely used in refractory glaucomas and NVG.

With Molteno implant there was 83 % success with an IOP less than 20 mmHg

²⁴___Krupin-denver valve has 67 % successes rate with IOP less than 24 mmHg

²⁵. Ahmed and Baerveldt glaucoma valve implant may also used in surgical management of refractory NVG ²⁶.

The problems with all stent and shunt procedures in the treatment of NVG are the same. They is early postoperative hypotony, blockage of the internal fistula, blockage of the external site, and a vigorous postoperative fibrous encapsulation response ^{26 27}. Postoperative hypotony with flat anterior chamber is the commonest complication. Modification of Molteno technique using two stages²⁴, or suture intubation of the silicone tube²⁸ and introduction of valved implants (e.g., Krupin and Ahmed) are valid attempts to avoid early postoperative hypotony.

Obstruction of internal fistula is unique to all drainage devices and is common in NVG as intraocular bleeding and fibrovascular membranes can block the opening of the tube.

CILIODESTRUCTIVE PROCEDURES

CYCLOCRYOTHERAPY

When medical therapy does not provide symptomatic relief in end-stage NVG, cyclodestructive procedures should be considered. Cyclocryotherapy produces hypotensive effect by destruction of secretory ciliary epithelium²⁹.

There is about 63% of successes in controlling IOP but about 40% goes for hypotony³⁰. Phthisis bulbi is another common complication. Standardization of treatment protocol was introduced in 1973. Only 180 degrees of ciliary body is treated at one time, employing six spots of freezing, 2.5mm posterior to limbus³¹. If saving functional vision is not a factor, and relief of pain is the main consideration, then cyclocryotherapy is useful. So it should be reserved for the final effort in the treatment of NVG.

CYCLODIATHERMY

The successes rate of IOP less than 25 mmHg equals the phthisis rate. Cyclodiathermy appears to be more destructive than cyclocryotherapy.

LASER CYCLOPHOTOCOAGULATION

Using slit-lamp or fibreoptic delivery system, mainly the diode and also ND:YAG lasers are used. IOP can be controlled and visual results are poor. Standardization protocol for NVG is not established. Direct visualization and treatment of the ciliary processes is done through transpupillary route using endoscope or a goniolens or an intraocular procedure with vitrectomy.

High intensity ultrasonography and intraocular carbon dioxide photocoagulation have also been used to destroy ciliary processes. No standardization protocol been established for these procedures.

RETROBULBAR INJECTION

Retrobulbar alcohol or chlorpromazine injection has been reported with long-standing relief of pain³².

PROPOSED TREATMENT ALGORITHM

EYES WITH USEFUL VISION

1. Treatment of the underlying retinal ischemia and / or inflammation.
2. Appropriate retinal ablation procedure
3. Residual glaucoma management

MEDICAL

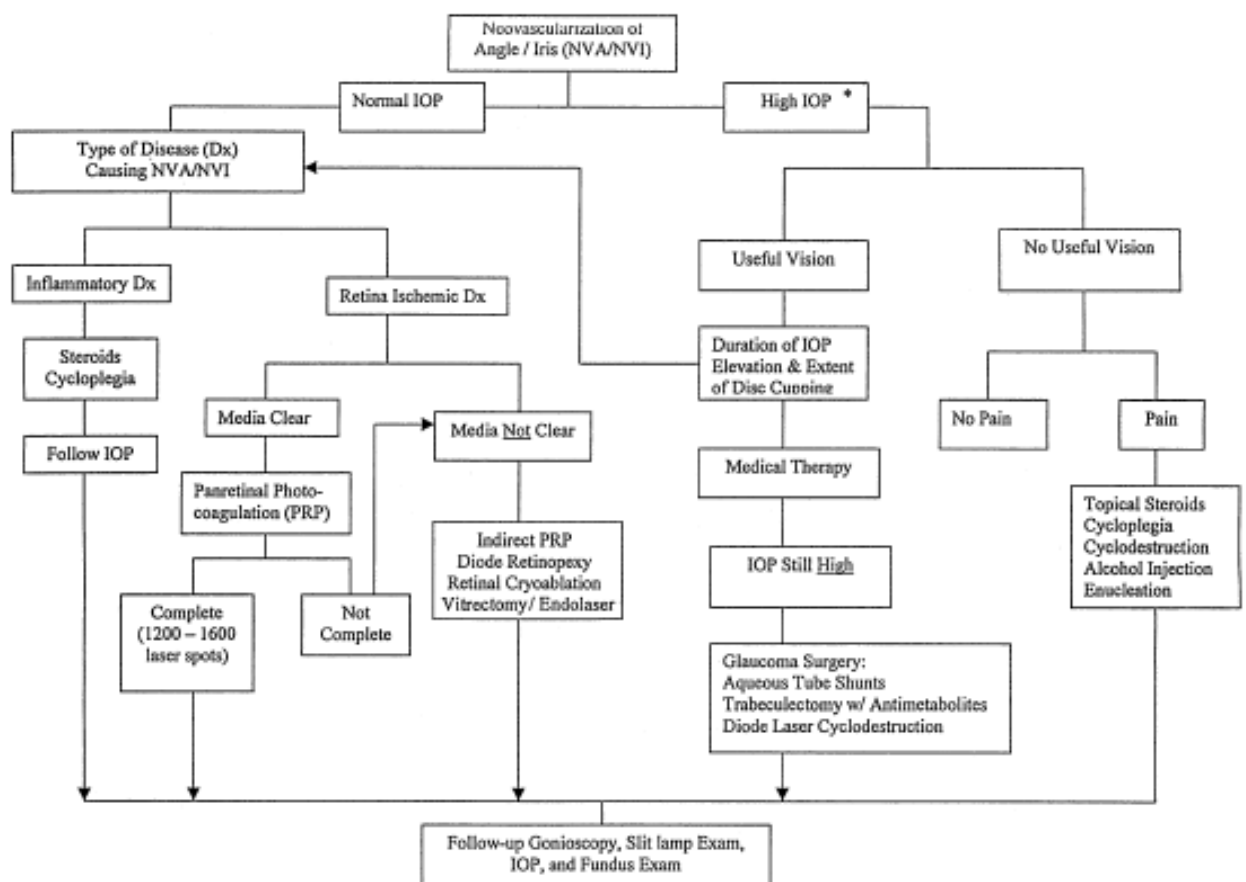
- Aqueous production reducing topical and systemic.

SURGICAL

- Trabeculectomy with Mitomycin C
- Aqueous tube shunt implant
- Diode laser cyclophotocoagulation

EYES WITH NO USEFUL VISION

In eyes with no useful vision, the goal is patient comfort. Initially, medical treatment and in recalcitrant cases surgical intervention like cyclodestruction, retrobulbar alcohol injection and enucleation is done.



Treatment algorithm for neovascular glaucoma

RECENT CONCEPTS OF TREATING NVG BY ANTI VEGF

Since there are various modalities in the treatment of NVG, all are aimed at reducing the IOP to make the patient comfortable without pain and preserve useful vision available. Even though PRP is the golden standard and is useful in reducing the retinal ischemia, it destroys the retinal tissue. In patients with media opacity such as cataract or vitreous hemorrhage, it is difficult to perform PRP.

Due to the presence of ongoing pathology of retinal ischemia which induces the neovascularization, the medical management becomes intractable and the surgical procedures has high failure rate, a new modality of counteracting the angiogenesis factor is thought off.

Therefore, direct targeting of VEGF with anti-VEGF pharmacotherapy may be another possible therapeutic strategy to treat NVG ³³.

IVB facilitates regression or resolution of anterior segment neovascularization to stabilize IOP in early-stage NVG with an open angle and it may improve the quality and safety of antiglaucoma surgery in advanced NVG with angle closure, thus providing long term IOP control.³⁴

Intravitreal Bevacizumab (Avastin) leads to rapid regression of iris and angle neovascularization in the management of NVG³⁵.

HISTORICAL INTERESTS IN THE DEVELOPMENT OF ANTIANGIOGENESIS

As early as 1948, Michaelson postulated the existence of vasoformative factor, “X” factor, that controlled the normal development of the new vessels during embryogenesis^{5 36}. Aston and associates in 1954 suggested that excess of this factor “X” caused retinal neovascularization in retinal ischemia of ROP.

In 1971, Folkman proposed that anti-angiogenesis might be effective in anticancer therapy³⁷.

In 1983, Sengar, reported the partial purification from the conditioned medium of guinea pig tumor cell line of “Vascular permeability factor” (VPF), a protein that produced vascular leakage in the skin³⁸.

In 1989, “Vascular Endothelial Growth factor” (VEGF), an endothelial cell specific mitogen, from medium conditioned by bovine pituitary follicular cells was isolated³⁹.

Sengar and collaborators independently reported the isolation and sequencing of VPF⁴⁰. cDNA cloning of VEGF, by Ferrara’s group and of VPF, by Connolly’s group, showed that VEGF and VPF were same molecule.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)

VEGF refers to 4 homodimeric polypeptides produced through alternative splicing of messenger RNA (mRNA). It is a potent angiogenesis and permeability enhancing factor made in retinal cells and VEGF, mRNA levels are dramatically increased during hypoxia.

VEGF is essential for normal embryonic vasculogenesis and angiogenesis. Plasminogen activation is important in regulating the activity and bioavailability in physiological and pathological angiogenesis⁴¹.

VEGF increases vascular permeability and is important in inflammation and in other pathological conditions⁴². VEGF is mitogenic and the primary target is the endothelial cells⁴³.

VEGF induces a potent angiogenic response in a variety of *in vivo* models⁴⁴. Action of VEGF is to promote the growth of vascular endothelial cells derived from arteries, veins and lymphatics⁴⁵.

VEGF has significant homology to A and B chains of PDGF⁴⁶. VEGF-A is a prototype member of a gene family that includes Placenta Growth Factor, VEGF-B, VEGF-C, VEGF-D and orf virus-encoded VEGF-E6.

The gene encoding human VEGF- A is organized in eight exons, separated by seven introns⁴⁷.

Alternative exon splicing results in the generation of four principle isoforms namely VEGF-121, VEGF-163, VEGF-189 and VEGF-206, that have 121, 165, 189 and 206 amino acids respectively following single-sequence cleavage.⁴⁶ Less frequent splice variants have been also reported, including VEGF-145, VEGF-183, VEGF-162, VEGF-165b.

Alternate splicing regulates the bioavailability of VEGF. VEGF-121 fails to bind Heparin and is freely diffusible protein. VEGF-165 is secreted, but a significant fraction remains bound to the cell surface an extra cellular matrix and is the most physiologically relevant isoform. Plasmin is able to cleave VEGF-165.

VEGF RECEPTORS

VEGF receptors are present on retinal capillary endothelial cells. There are two VEGF receptor tyrosine kinases: VEGF-R1, also known as Flt-1 and VEGF-R2, also known as Flk-1. **VEGF-R2** is the major mediator of the mitogenic, angiogenic, and permeability enhancing effect ⁴⁸. **VEGF-R1** is not directly involved in mitogenesis and angiogenesis, may function as a “decoy” receptor that sequesters VEGF and prevents its interaction with VEGF-R.2. Neuropilin-1 (NP-1), seems to present VEGF-165 to VEGF-R2 in a manner that potentiates VEGF-R2 signaling ⁴⁹.

EXPRESSION OF VEGF

VEGF mRNA expression is induced by exposure to low pO₂. Oxygen tension has a key role in regulating the expression of a variety of genes, including VEGF⁵⁰.

ANTI VEGF

Administration of VEGF inhibitors delays follicular development and suppresses luteal angiogenesis in primates ⁵¹.

VEGF-164 blockade led to a significant inhibition of pathological Neovascularization with little or no suppression of revascularization and physiological Neovascularization ⁵².

AVASTIN (BEVACIZUMAB)

Avastin (Bevacizumab) is a recombinant humanized monoclonal immunoglobulin G-1 (IgG), antibody that inhibits human vascular endothelial growth factor. It was approved by the United States Food and Drug Administration on 26th February 2004 as a first line treatment of metastatic colorectal cancer. Bevacizumab is composed of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N-linked oligosaccharide and has a molecular weight of approximately 149,000 daltons.

Avastin is a clear to slightly opalescent, colorless to pale brown sterile solution for intravenous (IV) infusion. Avastin is available in 100 mg and 400 mg single dose vials, containing 4 ml and 16 ml, respectively of bevacizumab (25 mg/ml). Avastin also contains a triose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

PHARMACOLOGY

MECHANISM OF ACTION

Avastin is an antineoplastic agent containing the active ingredient, bevacizumab. Avastin inhibits the binding of VEGF to its receptors, Flt-1 (VEGF-R1) and KDR (VEGF-R2), on the surface of endothelial cells. Avastin binds to and neutralizes all human VEGF-A isoforms and does not neutralize other members of VEGF family gene, like VEGF-B or VEGF-C.

Neutralizing the biologic activity of VEGF reduces the vascularization of tumors, thereby inhibiting tumor growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive antitumor activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and micro vascular permeability was reduced.

PHARMACOKINETICS

Nontoxic to the retina and optic nerve at 2.5 mg dose.⁵³ The pharmacokinetics of Bevacizumab were characterized in patients with various types of solid tumors. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterized by a low clearance, a limited volume of the central compartment (V_C), and a long elimination half-life.

Terminal half-life of Avastin in humans is 17 – 21 days. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and subject age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]).

Low albumin and high alkaline phosphatase levels are generally indicative of disease severity and tumor burden. Bevacizumab clearance was approximately 20% higher either in subjects with low levels of serum albumin or in subjects with elevated alkaline phosphatase levels when compared with the typical subject with median values of albumin and/or alkaline phosphatase.

ELIMINATION

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk. The value for clearance is, on average, equal to 0.207 and 0.262 L/day for female and male subjects, respectively. After correcting for body weight, male subjects had a higher bevacizumab clearance (+26%) than females. According to the bi-compartmental model, the initial half-life (α) is 1.4 days for both sexes, and the terminal (β) half-life estimate is 20 days for a typical female subject and 19 days for a typical male.

ADVERSE EFFECTS

Adverse effects Includes thrombosis, bleeding, proteinuria and hypertension Haritoglou et al in his study on 51 patients with diffuse diabetic macular edema. treated with a 0.05-mL injection containing 1.25 mg of bevacizumab and followed up for 6 weeks⁵⁴. Mean visual acuity increased at 6 weeks after injection ($P = 0.001$), with some regression after 12 weeks. Mean retinal thickness decreased at 2 weeks ($P = 0.002$), at 6 weeks ($P = 0.001$), and at 12 weeks ($P = 0.001$) and concluded that even in cases of diffuse diabetic macular edema not responding to previous treatments such as photocoagulation, intravitreal injection of triamcinolone, or vitrectomy, improvement of visual acuity and decrease of retinal thickness could be observed after intravitreal injection of bevacizumab

Costa et al in a study on 7 eyes with macular edema associated with ischemic central or hemi central RVO treated with intravitreal injections of 2.0 mg (0.08 ml) of bevacizumab at 12-week intervals, fluorescein leakage was observed in the macula and affected retinal quadrants in all seven eyes⁵⁵. No patient had a decrease in BCVA and concluded that Intravitreal bevacizumab injections were well tolerated and associated with short-term BCVA stabilization or improvement and favorable macular changes in all patients with ischemic RVO and associated macular edema.

Iturraldo et al in a retrospective study of 16 eyes with macular edema

due to CRVO treated with at least one intravitreal injection of bevacizumab 1.25 mg in 0.05 ml, intravitreal bevacizumab resulted in a significant decrease in macular edema and improvement in visual acuity⁵⁶.

Goff et al in a retrospective study of 51 patients treated with intravitreal bevacizumab for CNV from AMD, concluded that IVB for CNV from AMD resulted in a rapid decrease in OCT-measured retinal thickness in a majority of cases. Visual acuity also improved in this series, suggesting a potential corresponding visual benefit⁵⁷.

Michel et al in a study evaluating the short-term safety of systemic bevacizumab on visual acuity (VA), sub foveal choroidal neovascularization (CNV) in patients with neovascular age-related macular degeneration (AMD) there was no serious ocular or systemic adverse events⁵⁸. They concluded that overall, bevacizumab therapy was well tolerated, with an improvement in VA, OCT, and angiographic outcomes.

AVASTIN IN TREATMENT OF NEO VASCULAR GLAUCOMA

Wakabayashi et al in a retrospective, study on 41 eyes with INV or NVG secondary to ischemic retinal disorders concluded that Intravitreal bevacizumab is well tolerated, effectively stabilized INV activity, and controlled IOP in patients with INV alone and early-stage NVG without angle closure. In advanced NVG,

IVB cannot control IOP⁵⁹.

Vatavukz et al concluded that Bevacizumab seems to be a useful adjunct to PRP in the treatment of neovascular glaucoma⁶⁰.

Milko et al in a retrospective study of 6 patients with NVG who had received 1.25 mg/0.05 ml IVB. Diode laser cyclophotocoagulation was carried if pressure not controlled sufficiently by topical medication and followed for period of 4 to 16 weeks. IVB resulted in marked regression of anterior segment Neovascularization and relief of symptoms within 48 hours⁶¹

Deepa et al in a study on 14 eyes of 12 patients treated with IVB and PRP concluded that long-term preservation of open angle and IOP control in eyes receiving bevacizumab along with PRP stressed that NVG is still associated with poor visual acuity outcomes⁶².

Moataz et al in a study on 6 cases of NVG studied and followed for a period of 3–19 months (average, 9.7 months) after 1.25 mg (0.05 cc) of IVB followed by pan retinal photocoagulation (PRP) approximately 1 week later showed complete regression of iris and anterior chamber angle neovascularization in all patients. They concluded that IVB may be a valuable addition in the treatment of NVG by hastening the resolution of anterior segment neovascularization, improving the results of glaucoma surgeries, and appears to give long-term control when used in combination with PRP⁶⁴.

Other anti VEGF agents:⁷⁰

- Pegaptanib Sodium
- Ranibizumab
- VEGF trap

PEGAPTANIB SODIUM

Pegaptanib sodium is an anti VEGF aptamers. Aptamers are oligonucleotides designed to bind with specific molecular targets. This agent is a polyethylene glycol (PEG) – conjugated oligo nucleotide that binds specifically to VEGF 165 isoform⁶⁹.

However because of its selective binding it is no longer considered to be as effective as Ranibizumab and Bevacizumab.

RANIBIZUMAB

Lucentis is a second generation antibody with reduced size that allows it to penetrate all of the retinal layers. The drug is a 2 – part humanized monoclonal antibody fragment against VEGF. It is an antigen binding murine derived epitope with a non binding human sequence added to reduce the antigenicity in primates. It binds to 121, 165 and 110 isoforms. It is approved for use in exudative ARMD.

Anecortave acetate is a corticosteroid derivative found to inhibit angiogenesis induced by basic fibroblastic growth factor (b FGF) and VEGF as well as other known stimulators of angiogenesis .

Materials and methods

MATERIALS AND METHODS

A prospective randomized study on 15 eyes of 15 patients with neovascular glaucoma attending the Glaucoma service at Institute of Ophthalmology Joseph Eye Hospital, Tiruchirapalli, between May 2008 to October 2009 was conducted. Eyes receiving one or more doses of intravitreal Bevacizumab were studied.

Informed consent was obtained from all patients after discussing the benefits and potential risks and alternative treatment. The procedures used conformed to the Tenets of the declaration of Helsinki and was approved by the ethics committee board of the institute.

INCLUSION CRITERIA

1. Patient with a clinical diagnosis of neovascular glaucoma by slit lamp evidence of neovascularization of iris/ and angle and elevated IOP.
2. Neovascular glaucoma not controlled by maximum medical therapy
3. Presence of underlying cause for retinal ischemia i.e. CRVO, Vitreous Hemorrhage, advanced PDR
4. Patient willing for and receiving IVB
5. No systemic contraindication for IVB
6. Follow up for at least 6 months

EXCLUSION CRITERIA

1. Systemic contraindication for intravitreal injection
2. Medically controlled NVG
3. Patient lost to follow up
4. NVG due to intraocular tumor
5. Anterior segment pathology interfering with IOP measurement i.e. pterygium

All patients underwent a complete clinical examination including best corrected visual acuities with Snellen chart, slit lamp bio-microscopic examination, IOP measurement using Goldmann applanation tonometer, gonioscopic examinations using Goldmann 3-mirror lens. If necessary, fundus fluorescein angiography and fundus examination was done by a retina consultant to evaluate the pre existing cause of ischemic retinal disorder. Preoperative pan retinal photocoagulation and postoperative PRP was given whenever necessary. B-scan Ultrasonography to evaluate posterior segment status done to patients wherever the media is hazy. A complete systemic examination was done by an internist and fitness for intravitreal injection was obtained. IOP was well controlled by maximal medical therapy before IVB was given.

Commercially available bevacizumab (Avastin Genentech, Inc., South San Francisco, CA) (Avastin 25mg/ml) was prepared for each patient and was placed in tuberculin syringe with 26 gauge needle.

Under topical anesthesia with 4% lidocaine eye drops and 1.25% povidone – iodine solution was instilled. Using a caliper a marking of 4mm from the limbus was made in the infero-temporal quadrant using gentian violet. 0.1ml of bevacizumab (1.25 mg) was injected intravitreally via pars plana under visualization wherever possible. Postoperatively Tab. Acetazolamide 250mg 3 times daily, Dorzolamide eye drop 3 times daily, Timolol maleate 0.5% eye drop twice daily, Prednisolone acetate 1% eye drop 4 to 6 times daily, Ofloxacin eye drop 0.3% 6 times daily with non steroidal anti-inflammatory tablet orally was advised in all .

Postoperative follow up examinations were performed 3 day, 1 week, 1 month, 3 months, 6 months after the intravitreal bevacizumab. During each follow up a complete clinical examination including best corrected visual acuities with Snellen chart, slit lamp bio-microscopic examination, IOP measurement using Goldmann applanation tonometre, gonioscopic examinations using Goldmann 3-mirror lens and the regression and recurrence of NVI, NVA and the need of additional or withdrawal of antiglaucoma medication was decided. Visual acuity was measured using Snellen acuity chart.

Complete success was defined as regression of NVI, relief of pain with tolerable IOP (\pm medical therapy) in the absence of phthisis and without the need of further surgical procedures.

When a surgical intervention such as cyclodestructive procedure like trans-scleral cyclophotocoagulation were performed, IVB therapy was considered failed.

Qualified success was defined as control of IOP and pain with additional non-destructive surgery such as trabeculectomy or additional pan retinal photocoagulation.

Statistical analysis was performed using SPSS (version 10.0) p value ≤ 0.05 was considered statistically significant.

Repeat injection of intravitreal bevacizumab was performed in patients if there is no regression or reappearance of NVI with increase in pain and symptoms despite, IVB, additional PRP and maximum tolerable anti-glaucoma topical medications.

CENTRAL RETINAL VEIN OCCLUSION

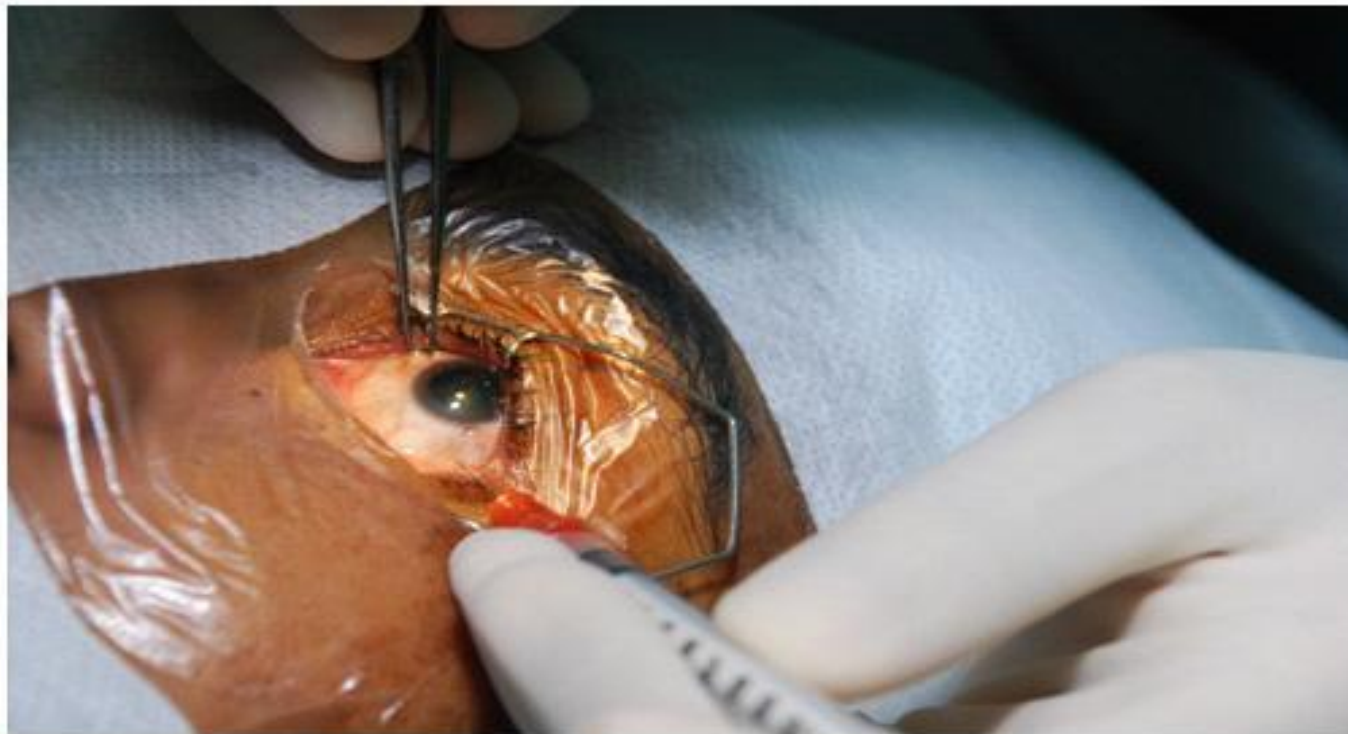
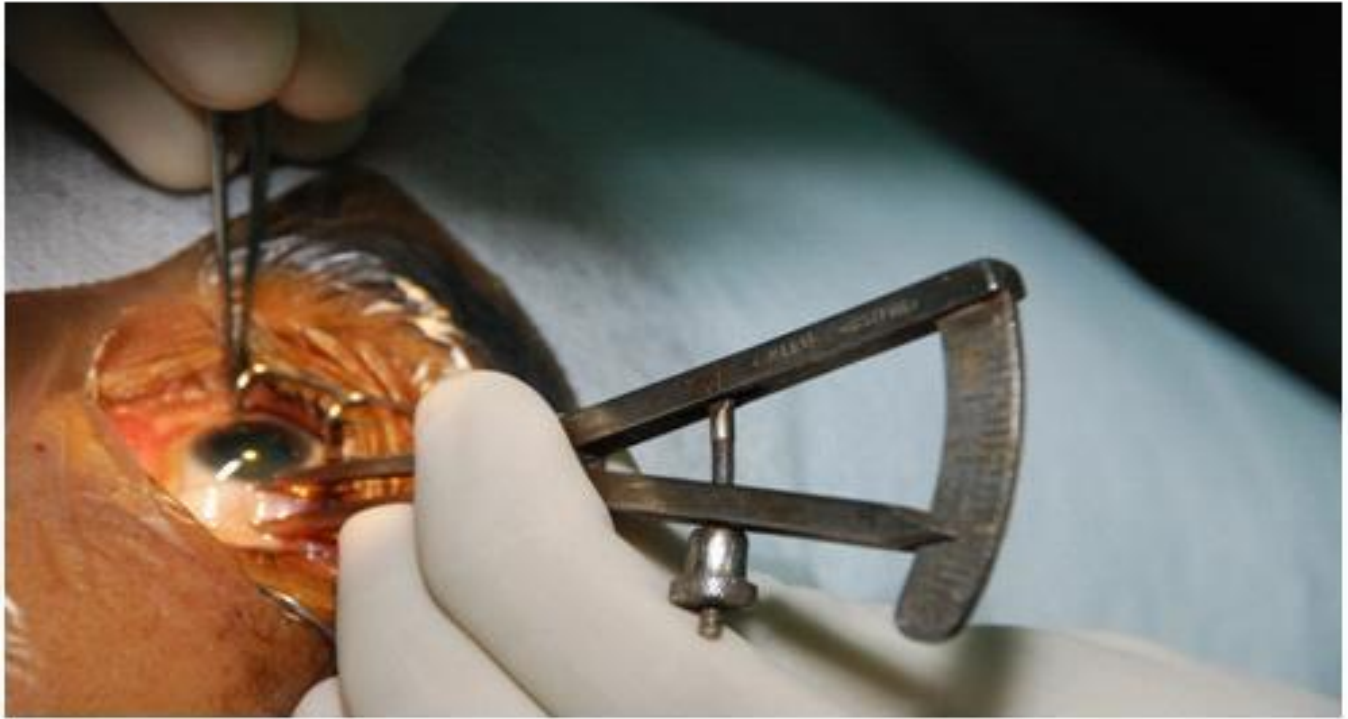


PDR WITH PRE RETINAL HEMORRHAGE





INTRAVITREAL AVASTIN - PROCEDURE



Results

RESULTS

Fifteen eyes of 15 patients were enrolled in the study out of which 11 were males (73.3%) and 4 were female (26.6%). Mean follow up period was 12.4 ± 3.52 months (6 –18 months). The mean age of the patients was 65.53 ± 8.57 yrs (range- 52-78 yrs).

Of these 15 eyes, 7eyes had NVG with open angles and 8 had NVG with angle closure. The patient demographics and baseline characteristics are shown in Table-1.

Underlying cause for neovascularization was retrospectively analyzed in all the 15 patients. In 11 patients, CRVO (73.33%) was the cause while in 2 patients CRVO along with PDR (13.3%) was found to be the cause. Posterior uveitis was the underlying cause in one (6.67%) and PDR alone was the causes for NVG for one eye (6.67%).

The mean IOP at the time of presentation in 15 eyes was 52.13 ± 12.93 mm Hg (range, 28-72). The mean IOP before IVB with medical management was 36.13 ± 11.92 mm Hg (range, 16–56) and at 1st visit after IVB was 34.8 ± 12.23 mm Hg (range, 16–64). The mean IOP at the end of follow-up (post IVB with medical management) was 37.20 ± 21.30 mm Hg. (Table - 2)

The mean reduction in IOP from the time of presentation to that before IVB was 16.00 ± 12.26 mm Hg was statistically significant, ($p=0.000$). The mean reduction in IOP recorded at first follow-up (after IVB) from that at presentation was 17.33 ± 11.07 mm Hg which was statistically significant ($p=0.000$). The mean reduction in IOP from the time of presentation to that at final follow-up (after IVB) was 14.93 ± 20.04 mm Hg which was also statistically significant, ($p=0.012$). (Table 3)

The mean reduction in IOP recorded at first follow up visit (after IVB) from that before IVB (after medical management) was 1.33 ± 13.51 mm Hg which was also statistically significant, ($p=0.708$)

At the first follow up, out of the fifteen eyes, only one (6.67%), experienced a rise in IOP, when compared to the IOP at the time of presentation. At the final follow up, out of 15 eyes, 5 eyes (33.33%) had persistent high IOP when compared to the IOP at the time of presentation.

Regression of NVI on first follow-up after IVB was studied in all 15 eyes and 13 out of 15 eyes (86.6%) had significant NVI reduction while 2 eyes (13.3%) had no signs of neovascular regression. Out of 15 eyes, 6 eyes (40%) had neovascularization involving the angle. All these cases showed regression of neovascularization at angle at first follow – up.

PRP was given before IVB in 7 eyes out of 15 (46%) and PRP post IVB in 9 eyes (60%). Three eyes (20%) received PRP both before and after IVB. One patient did not receive PRP at all.

Eyes which required repeat intervention was studied and 2 eyes out of 15 eyes (13.3%) required repeat IVB. Of the 2 eyes who received repeat IVB one eye was given IVB after 6 months and the other at 8 months.

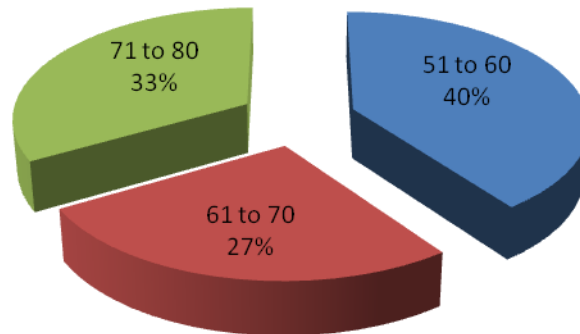
Four eyes underwent surgical intervention. Of these, 3 underwent trabeculectomy with cataract surgery and the remaining one eye had cyclocryotherapy.

Subjective reduction of pain and discomfort was seen in 14 eyes out of 15 (93.33%).

Improvement in visual acuity was seen in 2 eyes out of 15 (13.3%) while 13 eyes (86.6%) didn't show any significant improvement in VA when compared to the VA at the time of presentation. These 2 eyes, whose visual acuity improved were the ones who had underwent surgical intervention.

Adverse systemic and local complications related to IVB were monitored for all the patients throughout the study. Complications such as hypertension, myocardial or cerebral infarction, cataract - progression, uveitis, or endophthalmitis was not observed in any of the patients throughout the period of study.

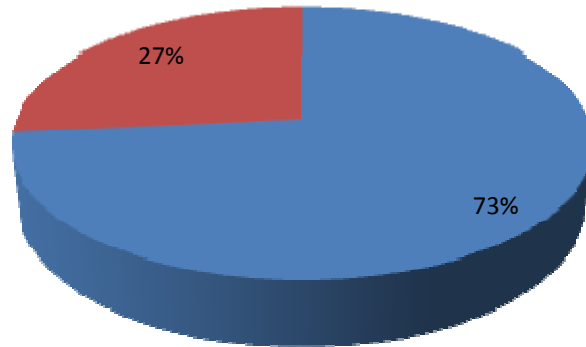
AGE DISTRIBUTION



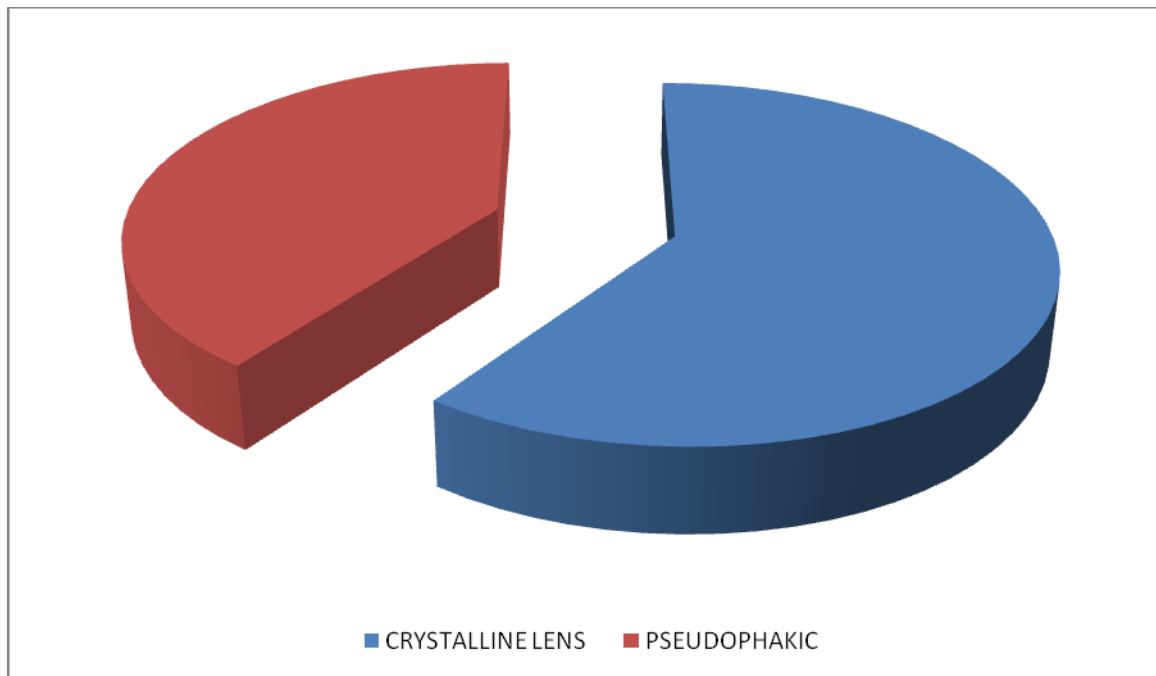
AGE(in yrs)	NO. OF CASES
51 to 60	6
61 to 70	4
71 to 80	5

GENDER DISTRIBUTION

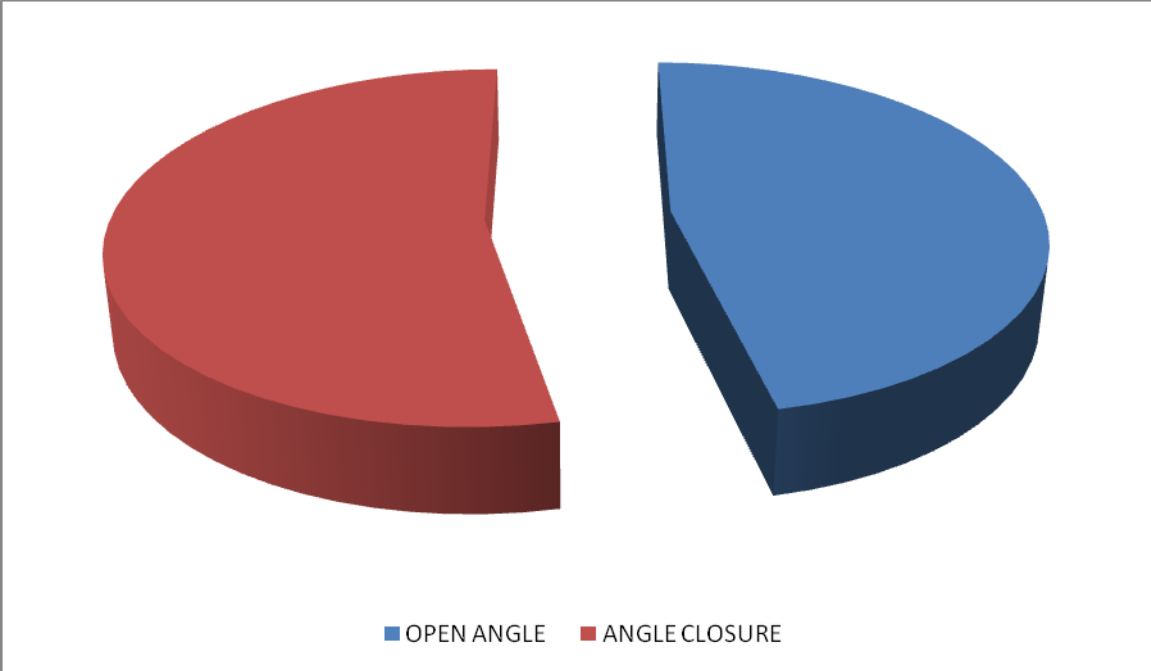
■ MALE ■ FEMALE



GENDER	NO. OF PATIENTS
MALE	11
FEMALE	4



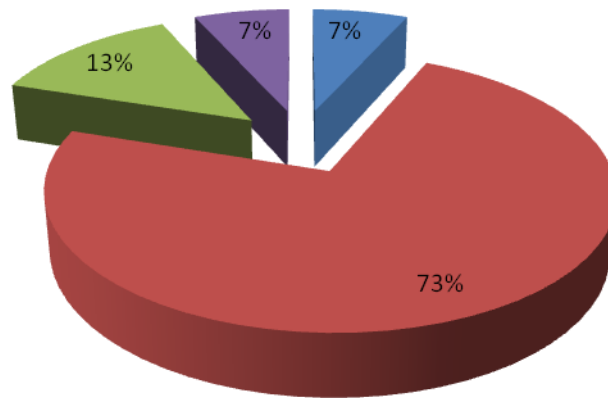
LENS STATUS	NO. OF EYES
CRYSTALLINE LENS	9
PSEUDOPHAKIC	6



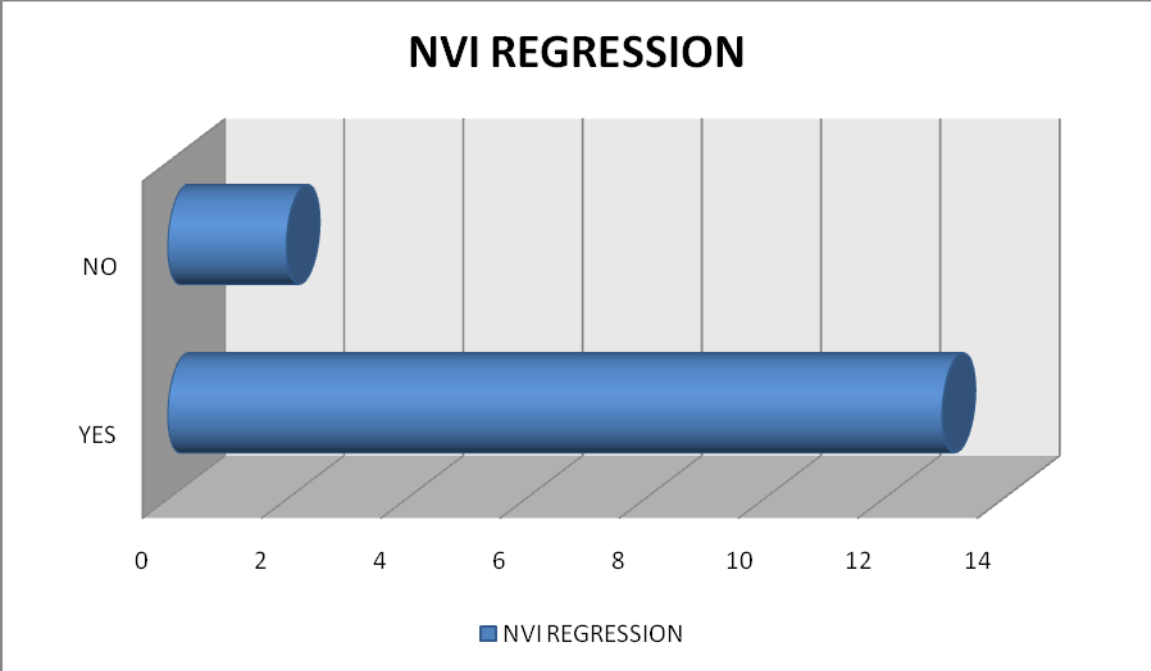
STAGE OF NVG	NO. OF EYES
OPEN ANGLE	7
ANGLE CLOSURE	8

CAUSE

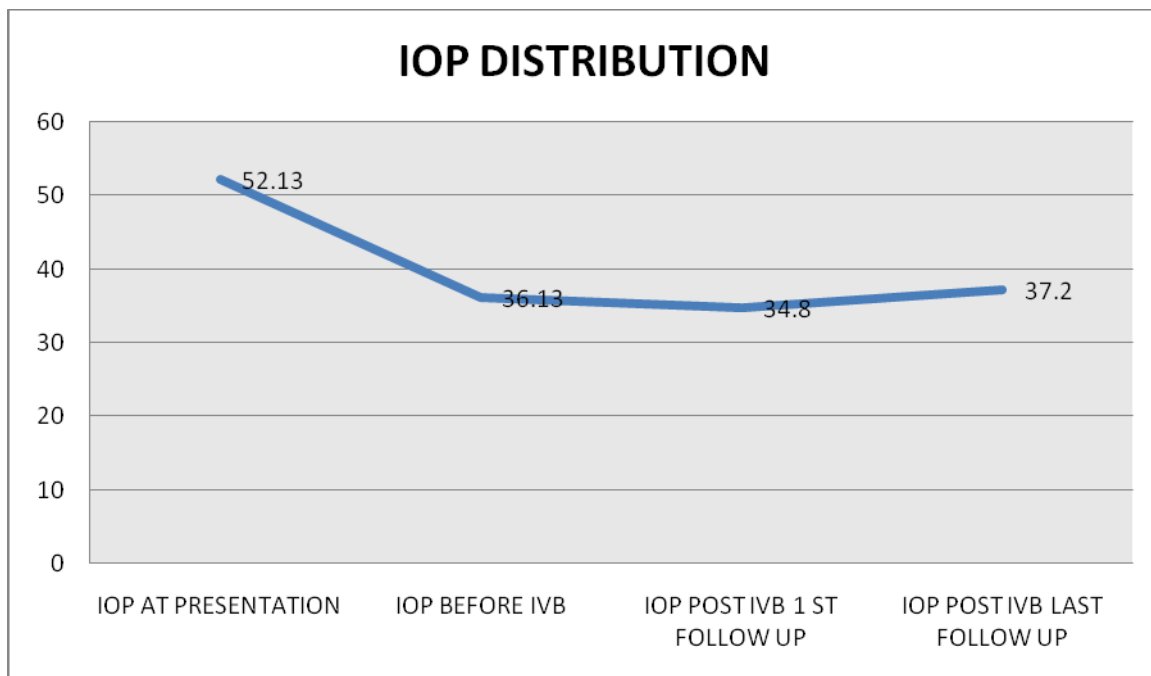
■ PDR ■ CRVO ■ PDR/CRVO ■ POSTERIOR UVEITIS



CAUSE	NO OF EYES
PDR	1
CRVO	11
PDR/CRVO	2
POSTERIOR UVEITIS	1



NVI REGRESSION	NO. OF EYES
YES	13
NO	2



	MEAN IOP (mmHg)
IOP AT PRESENTATION	52.13
IOP BEFORE IVB	36.13
IOP POST IVB 1 ST FOLLOW UP	34.8
IOP POST IVB LAST VISIT	37.2

TABLE - 1. DEMOGRAPHIC CHARACTERISTICS

Gender	
Males	11
Females	4
Mean age	65.53± 3.52 (52 - 78 years)
Follow up period	12.4±3.52 (6-8 months)
Stage	
Open angle	7
Angle closure	8
Lens status	
Crystalline lens	9
Pseudophakia	6
Underlying disease	
CRVO	11
PDR & CRVO	2
PDR	1
POST. UVEITIS	1

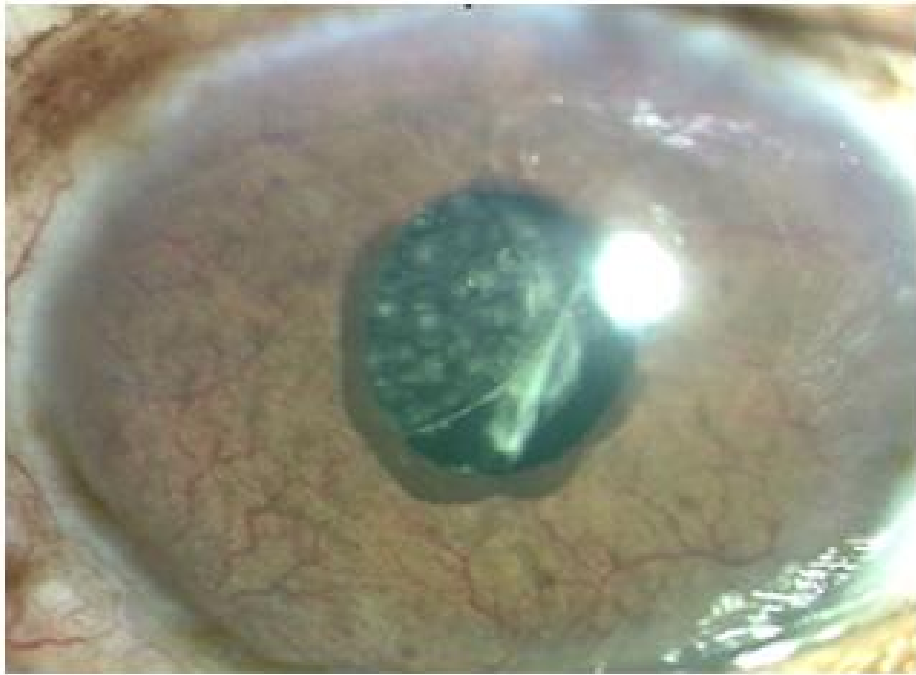
TABLE - 2. OBSERVATIONS OF MEAN IOP

No. of eyes = 15	Mean IOP (mmHg)
IOP AT PRESENTATION	52.13±12.92
IOP BEFORE IVB	36.13±11.91
IOP DIFF BET POST IVB AND AT FIRST FOLLOW UP VISIT	34.80±12.23
IOP DIFF BET POST IVB AND AT THE END OF FOLLOW UP	37.20±21.29

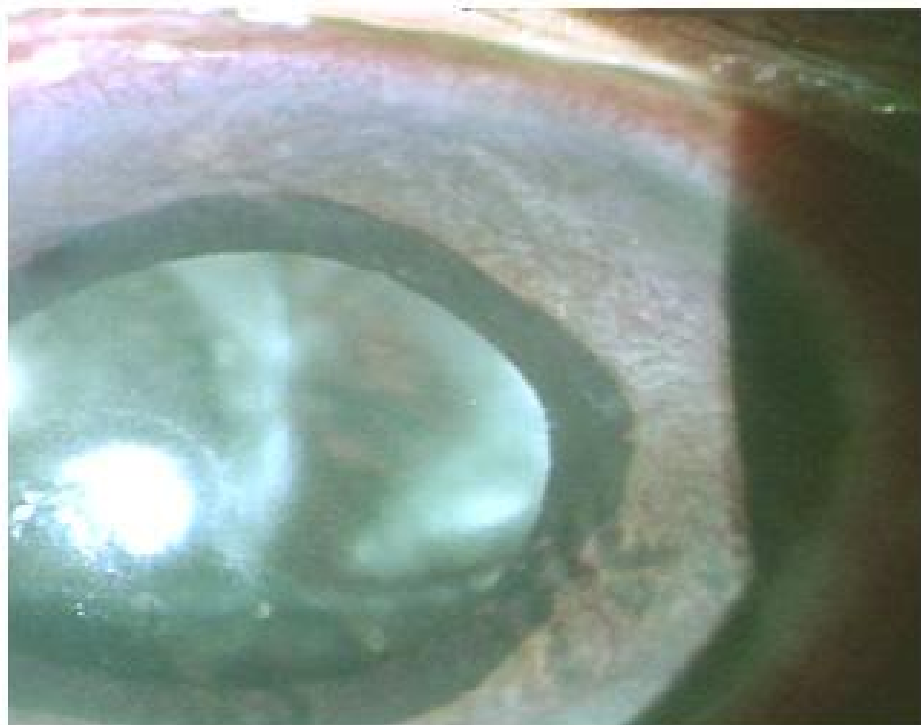
IOP DIFFERENCES	MEAN	P VALU E
IOP at presentation versus IOP Before IVB	16.000 ±12.25	0.000
IOP at presentation versus IOP After IVB 1st visit	17.333 ± 11.07	0.000
IOP at presentation versus IOP at end follow up	14.933 ± 20.04	0.012
IOP Before IVB versus IOP After IVB 1st visit	1.333 ± 13.51	0.708
IOP Before IVB versus IOP at final follow up	-1.067 ± 18.32	0.825
IOP After IVB 1st visit versus IOP at end follow up	-2.40 ±14.18	0.523

TABLE - 3. CHANGE IN IOP

NVI BEFORE IVB



REGRESSION OF NVI AFTER IVB



Discussion

DISCUSSION

In spite of various modalities available for the treatment of NVG, all are aimed at reducing the IOP and making the patient comfortable, without pain and preserve the useful vision available. Due to the presence of ongoing pathology of retinal ischemia which induces the neovascularization, as the medical management becomes intractable and the surgical procedures has high failure rate, new modalities of counteracting the angiogenesis factor are under trial.

Therefore, direct targeting of VEGF with anti-VEGF pharmacotherapy may be another possible therapeutic strategy to treat NVG ³³.

Recent encouraging results from several small case studies of IVB in the treatment of NVI, NVG or both has promoted, to consider the drug Bevacizumab (Avastin) as the first treatment of choice for NVG, secondary to underlying ischemic retinal disorders.

Fifteen eyes of 15 patients were enrolled in our study.

In our study male (73.3%) to female (26.6%) ratio was 11:4. In a similar study done by Wakabayashi et al ⁵⁹ the male (76.6 %) to female (23.4 %) ratio was 23:7.

In our study the mean age of the patients was 66.53 ± 8.57 (range 52 – 78). In a similar study by Wakabayashi et al⁵⁹ and Miliko E et al⁶¹ mean age of patients was 57.3 ± 9.6 yrs and 78.4 ± 7.5 yrs respectively.

In our study the underlying cause for neovascularization was retrospectively analyzed in all the 15 patients. In 11 patients, CRVO (73.33%) alone was the cause while in 2 patients CRVO along with PDR (13.3%) was found to be the cause. Posterior uveitis and PDR alone was the causes for NVG for one eye each (6.67%).

In a study by Wakabayashi et al⁵⁹ PDR (83%) was the major cause for NVG in contrary to our study where CRVO (73.3%) is found to be the major cause. In another study done by Miliko E et al⁶¹ the major underlying cause was CRVO (83.33 %). In the study done by Karl Ulrich et al 56.2 % had only CRVO as the primary cause while 43.8 % had PDR as the cause for NVG. A study done by Brown et al where he studied 208 consecutive cases of NVG diagnosed over 4 years, 36 % had CRVO, 32 % had DR and 13 % had Ischemic heart disease

The mean difference between the IOP at presentation and the IOP taken before IVB was 16 ± 12.26 mmHg. This was statistically significant

($p=0.000$). After giving IVB, the change in IOP was (17.33 ± 11.07 mmHg) highly significant. ($p=0.00$)

There was also a statistically different decrease in the IOP when comparing IOP at the time of presentation and that measured at the last follow up visit of the patient. (14.93 ± 20.04 mmHg) ($p=0.012$).

Similarly there was no significant difference in the IOP before IVB and after IVB to the IOP at the last follow up in our study ($p=0.825$) and ($p=0.523$) respectively. Wakabayashi et al ⁵⁹ in his study using IVB to treat NVG secondary to Ischemic retinal disease done in 41 eyes, found that the IOP decreased rapidly to nearly normal level to IVB mono therapy in 53 % of eyes with open angle NVG, but failed to control IOP (73 %) in the closed angle NVG group suggesting the efficacy of IVB in selected cases.

In our study NVI regression was seen in 86.66% during the first visit after IVB, 85.71 % (6 of 7eyes) in open angle stage and 87.5 % (7of 8 eyes) in angle closure stage. Wakabayashi et al ⁵⁹ showed NVI regression with successful normalization of IOP in 71% of patients with open angle stage and rapid NVI regression but failed to normalize the elevated IOP in most cases. Both the studies resulted in regression of NVI during the first week after the IVB. Yusuke et al who studied the regression of NVI after IVB injections in patients with PDR found regression of NVI in all the eyes from one week after injection. According to Gheith et al, there was a complete regression of iris and anterior

chamber angle neovascularization in all the six cases in his study on role of IVB in neovascular glaucoma

. In our study we have not monitored the role of PRP in the regression of neovascular changes. PRP before IVB was administered in 7 eyes out of 15 eyes (46%) and PRP post IVB in 9 eyes (60%). Three eyes (20%) received PRP both before and after IVB. One patient did not receive PRP at all. In a study done by Miliko et al ⁶¹, 2 eyes (33%) out of 6 eyes had pre IVB PRP, and 4 eyes (66%) out of 6 eyes had post IVB PRP. Deepa Vasudev et al ⁶¹ has also concluded in her study that long term preservation of open angle and IOP control was better with eyes receiving bevacizumab along with PRP.

Out of 6 patients who required repeat intervention, 2 eyes had to receive repeat IVB which was given in one eye after 6 months and the other at 8 months. The rest four underwent surgical intervention. Of these, 3 underwent trabeculectomy with cataract surgery and the remaining one eye had cyclocryotherapy. In the study done by Wakabayashi et al⁵⁹ 56.25% (18/32) of patients with neovascular glaucoma required repeat IVB injection. In his study 11 eyes out of 15 (73 %) required early surgical within one week of initial IVB injection, and a total of 14 eyes out of 15 (93 %) underwent surgery to stabilize the elevated IOP in the NVG with angle closure.

In our study subjective evaluation of pain and discomfort showed a decrease in 14 eyes out of 15 (93.33%). This can be compared by the study

done by Miliko et al in his study where all the patient had relieve of pain and discomfort.

Improvement in visual acuity was seen in 2 eyes out of 15 (13.3%) while 13 eyes (86.6%) didn't show any significant improvement in VA at the end of the study. These 2 eyes whose visual acuity improved had underwent cataract extraction with trabeculectomy. Studies done by Parrish et al and Tsai et al shows that not only IOP normalization but also visual stabilization is achieved by IVB.

Adverse systemic and local complications related to IVB were monitored for all the patients throughout the study and no adverse effect was found in all the cases in our study. MARINA trial recorded adverse effects like uveitis and presumed endophthalmitis in 1.7 % in anti VEGF treated subjects and other thrombo-embolic events such as MI, strokes and vascular deaths was found more in anti VEGF treated subjects than controls. Bevacizumab alone didn't cause adverse effects when systemically used along with chemo therapeutic agents in a study on efficacy on bevacizumab in colo-rectal cancer done by Hurvitz et al.

Our study shows use of IVB in NVG facilitates regression and resolution of anterior segment neovascularization, stabilization of IOP, relief of

pain and discomfort without causing any adverse side effects. However the effect of Bevacizumab on regression of NVI may be transient due to its short half life⁶⁷.

Conclusion

CONCLUSION

Iris neovascularization and subsequent development of neovascular glaucoma are serious complications in patients with proliferative diabetic retinopathy (PDR) and other ischemic retinal disorders.

Our study shows that there is a rapid regression of anterior segment neovascularization and IOP stabilization in patients with NVG. Intravitreal Bevacizumab is an effective primary therapeutic procedure as it facilitates regression and resolution of anterior segment neovascularization and IOP reduction and long term IOP stabilization in both stages of Neovascular glaucoma.

Adjuvant antiglaucoma medications and PRP are also indispensable in the effective control of IOP. In patients requiring filtering procedures, IVB improves the outcome of the procedure.

IVB also reduces symptoms like pain and discomfort in eyes with NVG, although in our study there was no improvement in visual acuity IVB seems to improve the outcome of the surgical interventions.

Therefore IVB promises to be an important intravitreal drug in the management of NVG.

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Proforma

PROFORMA

Case no:

Name: MRD no

Age: RE/LE

Sex

Systemic illness: Cardiac/DM/HT/Asthma/ Others

Pain and discomfort:

Treatment history:

PRP :

Antiglaucoma medications:

Ocular examination

Visual acuity

Uncorrected

BCVA

Slit lamp

Cornea

AC

Iris – NVI

Pupil

Lens

Applanation IOP

Gonioscopy – open angle, closed angle, angle NV

Fundus

Vitreous hemorrhage

Underlying ocular cause

Date of Avastin injection

1st injection :

Repeat injections:

Follow up: (during each follow up)

Visual acuity

S/L examination

IOP

Gonioscopy

Neovascular regression

Angle

Iris

Fundus

PRP

Treatment:

Medical

Surgical

Master charts

SI No	NAME	AGE	GENDER	ASSO SY DISEASE	PREX GL	RE	LE	BASE LINE VN	UND LY CAUSE	Pre PRP	Post IVB PRP	IOP AT PRES	I st IVB	I C P E e f I V E
1	Q	60	F	DM & HT			NVG	CFCF	PDR/CRVO	Yes	Yes	68	19 - 8 - 08	
2	T	78	M		PNAG		NVG	HM	post uvietis			72	27 - 7 - 09	
3	V	58	M	DM		NVG		HM	CRVO	Yes	Yes	40	28 - 6 - 09	
4	S	75	F	DM & IHD			NVG	NO PL	PDR	Yes		28	06/02/2009	
5	M	54	F	DM & HT		NVG		1 by 60	CRVO	Yes		72	06/10/2009	
6	D	74	M	DM & HT			NVG	PL +	CRVO	Yes		56	16 - 6 - 09	
7	A	76	M				NVG	NO PL	CRVO			62	7 - 4 - 09	
8	N	70	M	HT & IHD		NVG		PL +	CRVO		Yes	44	03/10/2008	
9	S	60	M	HT		NVG		NO PL	CRVO		Yes	50	18 - 2 - 08	
10	D	52	M	DM		NVG		PL +	PDR /CRVO		Yes	56	6 - 6 - 08	
11	R	70	M	DM &/ HT			NVG	1/2 by 60	CRVO		Yes	42	24 - 10 - 08	
12	N	65	M	DM & HT			NVG	1 by 60	CRVO	Yes	Yes	44	21 - 8 - 08	
13	A	57	M	DM & HT			NVG	1 by 60	CRVO		Yes	60	26 - 8 - 08	
14	S	72	F	DM			NVG	PL +	CRVO		Yes	42	21 - 4 - 08	
15	P	62	M	DM			NVG	NO PL	CRVO	Yes		46	09/02/2008	